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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/052,926	SAMPSON, JEFFREY R.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-35,67-70,72-101 and 144-149* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-35,67-70,72-101 and 144-149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 11, 2008 has been entered.

Applicant's amendment filed on July 11, 2008 is acknowledged and has been entered. Claims 1 and 67 have been amended. Claims 5, 36-66, 71, 102-143 have been canceled. Claims 1-4, 6-35, 67-70, 72-101, 144-149 are pending.

Claims 1-4, 6-35, 67-70, 72-101, 144-149 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL.

New Grounds of Rejection necessitated by amendment

The same references are applied in the rejection below, however the formulation of the obviousness rejection has been modified to more clearly address the claims as amended.

Claim Interpretation

While the term 'modified nucleotide' is addressed in the specification, the definition does not provide an explicit definition of the term. Instead, the term is defined in general terms such as "Modified bases (excluding A, T, G, C, and U) include for example, bases having a structure derived from purine or pyrimidine (i.e. base analogs). For example without limitation, a modified adenine may have a structure comprising a purine with a nitrogen atom covalently bonded to C6 of the purine ring as numbered by conventional nomenclature known in the art" (paragraph 17 of PgPub). The specification also teaches that the modified nucleotide has "a reduced ability to form base pairs with complementary modified or unmodified nucleic acids" (paragraph 10 of PgPub). Therefore, the term is being interpreted as reading on art directed to the inclusion of any kind of nucleotide that reduces hydrogen bonding or base pairing between 'natural' and modified oligonucleotide sequences.

The term 'at least one repeat of a nucleic acid' is not provided with an explicit definition in the specification. Instead, the term is defined in general terms such as "the present invention generates nucleic acid polymers for nanopore sequencing having multiple tandem repeats" (paragraph 8 of PgPub). Therefore, as the term requires at least one repeat and not tandem repeats, and without an explicit definition, the term is being interpreted as reading on art directed to any repeated nucleotide sequences in the nucleic acid.

The term "unstructured nucleic acid" is not defined in the specification. However, the specification teaches "Nucleic acid molecules with reduced secondary structure ("unstructured nucleic acids"; UNA) are generated by enzymatically incorporating modified nucleotide triphosphates that have a reduced ability to form base pairs with complementary modified and unmodified nucleotides" (paragraph 10 of PgPub). Therefore the term is being interpreted as reading on any nucleic acid which incorporates multiple modified nucleotide triphosphates that have a reduced ability to form base pairs.

Claim Rejections - 35 USC § 103

1. Claims 1-4, 8-34, 67-70, 74-100 and 144-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) and Kutyavin et al. (US Patent 5,912,340; June 1999). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

With regard to claim 1 and 67, Church teaches a method of sequencing a nucleic acid molecule comprising steps of:

providing two separate, adjacent pools of a medium and an interface between the two pools, the interface having a channel so dimensioned as to allow sequential nucleotide-by-nucleotide passage from one pool to the other pool of only one nucleic acid molecule at a time (Figure 1, where the method is depicted schematically; col. 1, line 35, col. 2, line 8, where two adjacent pools of medium are provided with an interface which is capable of interacting with individual monomer residues of a single polymer); producing a nucleic acid molecule with at least one

repeat of a nucleotide sequence to be determined (col. 11, lines 38-41, where nucleic acids with repeating identical bases are resolved, where 'punctuation' in the conductance is registered through a distinct/higher level of conductance between bases); placing the nucleic acid molecule in one of the two pools; and taking measurements as each of the nucleotides of the nucleic acid molecule passes through the channel so as to determine the sequence of the nucleic acid molecule (col. 1, line 35 to col. 2, line 8, where a single polymer is present in one of the two pools and interface dependent measurements are taken leading to characterization of polymers in the mixture and the method can be used to determine their sequence).

With regard to claim 2 and 68, Church teaches an embodiment of claim 1 and 67, wherein the nucleic acid is single- stranded (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA).

With regard to claim 3 and 69, Church teaches an embodiment of claim 2 and 68, wherein the nucleic acid is single-stranded DNA (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA).

With regard to claim 4 and 70, Church teaches an embodiment of claim 2 and 68, wherein the nucleic acid is single-stranded RNA (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA; col. 7, lines 55-60, where the polymer can comprise RNA).

With regard to claim 8 and 78, Church teaches an embodiment of claim 1 and 67, wherein the medium is electrically conductive (col. 2, lines 35-37, where the pools include electrically conductive medium, either the same or different composition; col. 2, lines 59-64, where the electrically conductive medium can be any medium, including an aqueous solution).

With regard to claim 9, 20, 28, 79, 90, 98, Church teaches an embodiment of claim 8, 19, 27, 78, 89, 97, wherein the medium is an aqueous solution (col. 2, lines 9-13, where the pools are liquids, usually aqueous solutions; col. 2, lines 59-64, where the conducting medium is any medium and preferably an aqueous solution).

With regard to claim 10, 14, 21, 23, 80, 84, 91, 93, Church teaches an embodiment of claim 8, 9, 20, 22, 78, 79, 90, 92, further comprising applying a voltage across the interface (col. 2, line 64 to col. 3, line 3, where voltage is applied across the barrier between the pools; col. 4, lines 57-67, where the passage is preferably voltage sensitive or voltage-gated).

With regard to claim 11, 15, 22, 24, 29, 30, 81, 85, 92, 94, 99, Church teaches an embodiment of claim 10, 14, 21, 23, 27, 28, 81, 84, 91, 93, 98, wherein ionic flow between the two pools is measured (col. 2, lines 35-47, where the conductive pools are separated by an impermeable barrier with an ion-permeable passage, an electrical potential between the two pools is established and ionic current is allowed to flow across the passage).

With regard to claim 12, 16, 25, 82, 86, 95, 100, Church teaches an embodiment of claim 11, 15, 24, 81, 85, 94, 97, wherein the duration of ionic flow blockage is measured (col. 4, lines 31-35, the characteristics of the polymer can be identified by amplitude and duration of individual conductance changes across the passage).

With regard to claim 13, 17, 26, 83, 87, 96, Church teaches an embodiment of claim 11, 15, 25, 81, 84, 94, wherein the amplitude of ionic flow blockage is measured (col. 4, lines 31-35, the characteristics of the polymer can be identified by amplitude and duration of individual conductance changes across the passage).

With regard to claim 18 and 88, Church teaches an embodiment of claim 1 and 67, wherein the nucleic acid polymer interacts with an inner surface of the channel (col. 6, lines 59-65, where the polymer passage through the interface results in monomer interactions with the interface that are sufficient to identify the monomers or the characteristics of the polymer; col. 20, lines 24-29, where "short duration blockades represent polymers that interact with the channel (e.g., loops of polymer that come to lie on the channel aperture)").

With regard to claim 19 and 89, Church teaches an embodiment of claim 18 and 88, wherein the medium is electrically conductive (col. 2, lines 35-37, where the pools include electrically conductive medium, either the same or different composition; col. 2, lines 59-64, where the electrically conductive medium can be any medium, including an aqueous solution).

With regard to claim 27 and 97, Church teaches an embodiment of claim 1 and 67, further comprising providing a polymerase or exonuclease in one of the two pools, wherein the polymerase or exonuclease draws the nucleic acid polymer through the channel (col. 7, lines 27-31, where a polymerase is fused with the pore to pull the nucleic acid through the channel; col. 12, lines 65-67).

Regarding claim 1 and 67, Church does not teach the steps wherein the nucleic acid molecule contains modified nucleotides that reduce secondary structure in the nucleic acid molecule.

With regard to claims 1 and 67, Morgan teaches a method comprising producing a nucleic acid molecule wherein the nucleic acid molecule contains modified nucleotides that reduce secondary structure in the nucleic acid molecule (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p.

5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and "probably resulted from loss of intermolecular base pairing")

and wherein the nucleic acid is an unstructured nucleic acid (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p. 5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and "probably resulted from loss of intermolecular base pairing").

With regard to claim 32 and 75, Morgan teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains modified guanosine and modified cytosine which are not able to form base pairs, wherein the modified guanosine is capable of forming a base pair with unmodified cytosine, and wherein the modified cytosine is capable of forming a base pair with unmodified guanosine (p. 5965, col. 1, where the lower stability of I-C as compared to G-C base pairs are discussed. In I-C base pairs there are 2 hydrogen bonds, while in G-C base pairs there are 3 hydrogen bonds present, however base pairing does occur, it is less stable).

With regard to claim 33 and 76, Morgan teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-aminoadenosine, 2-thiothymidine, inosine, and pyrrolopyrimidine (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p. 5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and "probably resulted from loss of intermolecular base pairing").

Neither Church or Morgan teach the inclusion of a modified adenosine or thymine. Kutyavin teaches modified bases that form less stable hydrogen bonds, which decreases melting temperature (Abstract).

With regard to claim 1, Kutyavin teaches at least two different complementary base pair analogues, wherein the at least two different complementary base pair analogs reduce secondary structure in the nucleic acid molecule and wherein the nucleic acid is an unstructured nucleic acid (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

With regard to claims 31 and 74, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains modified adenosine and modified thymine which are not able to form base pairs, wherein the modified adenosine is capable of forming a base pair with unmodified thymine, and wherein the modified thymine is capable of forming a base pair with unmodified adenosine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

With regard to claim 34 and 77, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-aminoadenosine, and 2-thiothymidine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine; Abstract, where it is noted that "the ODNs include modified bases of such nature that the modified base forms a stable hydrogen bonded base with the natural partner base, but

does not form a stable hydrogen bonded base pair with the modified primer" and notes "due to the lack of stable hydrogen bonding with each other, the matched pair of oligonucleotides have a melting temperature" which is 40oC or less).

With regard to claim 144 and 146, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains a modified thymine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

With regard to claim 145 and 147, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-thiothymidine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied and incorporated the modified nucleotides of Morgan to the practice of sequencing of nucleic acids as taught by Church to arrive at the claimed invention with a reasonable expectation for success. Church teaches the inclusion of a variety of modified nucleotides, but does not teach the specific inclusion of modified analogues to affect secondary structure of templates for sequencing. Morgan teaches a method that incorporates inosine residues in place of guanosine residues in transcripts and examines the effect on secondary structure, binding and elongation. Morgan finds that "the apparent molecular weights of the I-substituted products were altered as a consequence of the absence of G-C base pairs and

accompanying loss of ordered structure" (Abstract). Morgan teaches the substitution of guanosine with inosine and results in a change in secondary structure of the nucleic acid.

Furthermore, in view of the teachings of Kutyavin, it would have been obvious to replace adenine and thymine in the nucleic acids of the instant invention to include the 2-aminoadenine and 2-thiothymine of Kutyavin to include modified nucleotides, in addition to inosine, which are capable of reducing secondary structure. Kutyavin teaches, "the ODNs include modified bases of such nature that the modified base forms stable hydrogen bonded base pairs with the natural partner base, but does not form stable hydrogen bonded base pairs with its modified partner" and further teaches "the matched pair of oligonucleotides in accordance with the present invention do not form substantially stable hydrogen bonded hybrids with one another, as manifested in a melting temperature (under physiological or substantially physiological conditions) of approximately 40.degree. C. or less" (col. 1, lines 39-56). Therefore, Kutyavin teaches the inclusion of modified analogues for A and T which results in reduction in hydrogen bonding stability when the modified bases are included in a duplex nucleic acid. More plainly stated, the procedure for incorporating unstructured nucleotides disclosed by Kutyavin in view of Morgan renders the instantly claimed unstructured nucleic acids obvious because they each involve the synthesis of oligonucleotides in the presence of modified bases to produce nucleic acid with reduced ability to hybridize to complementary bases by reducing the ability to form Watson-Crick base pairing. This characteristic exists in intra-molecular hybridization within a strand as well as in inter-molecular hybridization between strands due to the physical characteristics of the modified nucleotides taught by Morgan and Kutyavin. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have

incorporated these additional analogues because the reduction in binding strength associated with both analogues would result in a reduction in secondary structure, to arrive at the claimed invention with a reasonable expectation for success. Finally, considering the teachings of Morgan, Church and Kutyavin, it would have been prima facie obvious to one of ordinary skill in the art to modify the secondary structure of template nucleic acid molecules prior to passing these molecules through a pore for establishing sequence identity using the known technique taught by Church to yield a predictable result.

2. Claims 6-7, 72-73 and 148-149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) and Kutyavin et al. (US Patent 5,912,340; June 1999) as applied to claims 1-4, 8-34, 67-70, 74-100 and 144-147 above, and further in view of Lizardi et al. (US Patent, 6,632,609; October 2003). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

Church in view of Morgan teach all of the limitations of claims 1-4, 8-34, 67-70, 74-100 and 144-147. Neither Church or Morgan teach that the nucleic acid is produced using a circular template. Lizardi teaches the synthesis and amplification of circular nucleic acid templates (Abstract).

With regard to claim 6 and 73, Lizardi teaches an embodiment of claim 1, wherein the nucleic acid is enzymatically produced using circular template that is single-stranded or double-stranded (Figures 1-4, where the open circle probe is single stranded and is ligated to form a circular template on the specific target nucleic acid and is therefore enzymatically produced).

With regard to claim 7 and 72, Lizardi teaches an embodiment of claim 6, wherein the circular template is single stranded (Figures 1-4, where the open circle probe is single stranded and is ligated to form a circular template on the specific target nucleic acid and is therefore enzymatically produced).

With regard to claim 148 and 149, Lizardi teaches an embodiment of claim 1 and 67, wherein said producing comprises contacting a circular template with a primer, a polymerase, nucleotides and modified nucleotides under rolling circle amplification conditions sufficient to produce said nucleic acid (col. 3, lines 1-32, where the amplification comprises these components; see also Figures 3 and 4, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of circular template production of Lizardi to the method of sequencing taught by Church to arrive at the claimed invention with a reasonable expectation for success. Church in view of Morgan teach sequence analysis of nucleic acids comprising modified nucleotides. However, neither Church or Morgan teach that the template comprises a circular template. Lizardi teaches "The DNA ligation operation circularizes a specially designed nucleic acid probe molecule. This step is dependent on hybridization of the probe to a target sequence and forms circular probe molecules in proportion to the amount of target sequence present in a sample" (col. 3, lines 10-14). Therefore, considering the circular templates taught by Lizardi, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the circular templates taught by Lizardi and this incorporation would have provided a predictable outcome with a reasonable expectation for success.

5. Claims 35 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) and Kutyavin et al. (US Patent 5,912,340; June 1999) as applied to claims 1-4, 8-34, 67-70 74-100 and 144-147 above, and further in view of Thorp et al. (US Patent 5,871,918; February 1999). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

Church in view of Morgan teach all of the limitations of claims 1-4, 8-34, 67-70, 74-100 and 144-147. Neither Church or Morgan teach the analysis of nucleic acids by electron tunneling.

With regard to claim 35 and 101, Thorp teaches an embodiment of claim 1 and 67, further comprising analyzing the nucleic acid molecules by electron tunneling (col. 9, line 18 to col. 10, lines 42, where in specific embodiments, the nucleic acid molecules are analyzed by electron tunneling).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the method of sequencing of Church to include the technique of electron tunneling detection of nucleic acid molecules as taught by Thorp to arrive at the claimed invention with a reasonable expectation for success. Church in view of Morgan teach the sequencing of nucleic acids, however neither teach the application of electron tunneling to the analysis of nucleic acid molecules. Thorp teaches the application of electron tunneling and notes that "correlation between the tunneling distance and the specific base paired with the preselected base is therefore established" (col. 10, lines 9-11). Therefore, as Thorp teaches that

electron tunneling may be used to analyze nucleic acids, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the method of sequencing of Church to include the technique of electron tunneling detection of nucleic acid molecules as taught by Thorp to arrive at the claimed invention with a reasonable expectation for success.

Response to Arguments

Applicant's arguments filed July 11, 2008 have been fully considered but they are not persuasive.

Applicant traverses the rejection of claims 1-5, 8-34, 67-71, 74-100 and 144-147 as being obvious over Church, Morgan and Kutyavin. Applicant argues at length that rejections and arguments based on the assertion that the modified nucleotides of Morgan and Kutyavin would inherently reduce secondary structure are incorrectly supported. Applicant asserts that "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" and notes "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art" (p. 12 of remarks). Applicant also states "at the time of filing of this application, unstructured nucleic acid (UNA) nucleotides were known and had been proposed for reducing the Tm of inter-molecular interactions between UNA-containing nucleic acids (see e.g. Kutyavin). Prior to the filing date, however, there was no recognition in the art that UNA nucleotides could decrease intra-molecular interactions within one nucleic acid" (p. 12 of remarks) and goes on to state

"conceptually, this can be thought of as a new use for UNA nucleotides" (p. 13 of remarks). Applicant goes on to point out how "the use of UNA nucleotides to decrease intra-molecular interactions is neither taught nor suggested by Kutyavin or the prior art" (p. 13 of remarks).

These arguments are not persuasive. First, regarding Applicant's arguments regarding the lack of support for the assertion of inherency, it is noted that the rejection has been reformulated above to more clearly state the technical basis for the inherent features of the modified nucleotides, present in Morgan and Kutyavin in combination, that would necessarily result in reduced secondary structure. As noted in the rejection stated above, and restated here, Kutyavin makes clear that the modified nucleotides, when paired with each other, do not form stable hydrogen bonded base pairs with its modified partner and also notes that this results in a reduction in melting temperature. While Kutyavin teaches embodiments where these modified nucleotides are incorporated in an inter-molecular setting, Kutyavin makes no distinction between the effect on the binding partnership in an inter-molecular as opposed to intra-molecular setting. The modified nucleotides are present in the same form and structure in either an intermolecular or intra-molecular format and would be affected equally by the descrease in hydrogen bonding stability in either context. Therefore, it is viewed that the presence of the modified nucleotides of Morgan and Kutyavin would necessarily result in a reduction in secondary structure due to the decrease in hydrogen bonding in these modified nucleotides as taught specifically by Kutyavin. Therefore, in the absence of evidence that the decrease in stability of hydrogen bonding in the bonding of these modified nucleotides affects nucleotides in an intra-molecular bonding setting differently than it does in an inter-molecular setting, the

modified nucleotides of Morgan and Kutyavin necessarily and inherently affect the binding of inter-molecular and intra-molecular bonds in the same way.

Regarding Applicant's arguments towards the lack of recognition of the affect on intra-molecular bonding, or the concept of a new use of unstructured nucleic acids, these arguments are also not persuasive.

Regarding this issue, the MPEP 2111.04 I,

> **SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY**
>
> "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." *Id.*< See also MPEP § 2112.01 with regard to inherency and product-by-process claims and MPEP § 2141.02 with regard to inherency and rejections under 35 U.S.C. 103.

Further regarding this issue, the MPEP 2111.04 II also states (in part),

> **II.INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION**
>
> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)

Therefore, while Applicant's arguments are appreciated, the argument that Applicant found "a new use for UNA nucleotides" is not a patentable feature of Applicant's invention. The modified nucleotides have an inherent feature which results in a decrease in hydrogen bonding stability. While this may have been identified first in an intermolecular hybridization reaction, it is not required that the prior art must explicitly state all of the other contexts in which this effect would be observed, in an

intramolecular hybridization, for example, for the reasons stated in the MPEP above. Therefore, for the reasons stated above, Applicant's arguments are not persuasive and the rejections are maintained.

Applicant also traverses the rejection of the claims over Church, Morgan and Kutyavin and further in view of Lizardi or further in view of Thorp. These rejections are traversed largely for the reasons asserted above regarding the combination of Church, Morgan and Kutyavin. These arguments are not persuasive for the reasons stated above. The rejections are maintained.

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Stephanie K. Mummert/
Examiner, Art Unit 1637